



The use of combined oral contraceptives and their relationship with venous thromboembolism

O uso de contraceptivos orais combinados e sua relação com o tromboembolismo venoso

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ABSTRACT

Venous thromboembolism (VTE) is the third most frequent cause of acute cardiovascular syndrome in the world, It is determined by the formation of a clot in one or more blood circulation pathways, in which various etiological factors are related to this hemostatic imbalance, and combined oral contraceptives (COCs) may even be associated with its appearance.

Keywords: Oral Contraceptives, VTE, Thrombosis.

RESUMO

O tromboembolismo venoso (TEV) é a terceira causa mais frequente de síndrome cardiovascular aguda no mundo, determinado pela formação de um coágulo em uma ou mais vias de circulação sanguínea, no qual vários fatores etiológicos relacionam-se a este desequilíbrio hemostático, podendo, inclusive, os anticoncepcionais orais combinados (COCs) estarem associados ao seu surgimento.

Palavras-chave: Contraceptivos Orais, VTE, Trombose.

1 INTRODUCTION

Venous thromboembolism (VTE) is the third most frequent cause of acute cardiovascular syndrome in the world, It is determined by the formation of a clot in one or more blood circulation pathways, in which various etiological factors are related to this hemostatic imbalance, and combined oral contraceptives (COCs) may even be associated with its appearance. COCs are a compound formed by combining a progestogen with an estrogen which, in addition to preventing pregnancy, aims to benefit women in situations of dysmenorrhea, menorrhagia and symptoms of premenstrual tension. However, recently, several cases have shown a causal link between the use of COCs and the onset of vascular disorders such as VTE. Thus, the problem in question becomes relevant, given that most of the women who use this medication are



young, of reproductive age and healthy, urging the need to reduce vascular complications regarding the use of combined contraceptives, so that the promotion of increased female well-being does not cause intense side effects.

2 OBJECTIVE

To analyze the current body of science on the use of combined oral contraceptives and their relationship with venous thromboembolism.

3 METHODOLOGY

This is an integrative literature review carried out in the Virtual Health Library (VHL), using the Medical Literature Analysis and Retrieval System Online (MEDLINE) database, using the descriptors "thrombosis and contraceptive agents", with the filters: full text, English, combined oral contraceptives, in the last 5 years (2018-2022).

4 DEVELOPMENT

Of the 1,572 articles initially found, after applying the eligibility criteria, there was a reduction to 19 publications and, after excluding 9 articles due to incompatibility with the proposed topic and the presentation of case studies, which were considered too particular for the study, a final corpus of 10 articles was obtained for analysis, which were selected for similarities in two thematic axes: (I) Understanding the pathophysiology of VTE associated with the use of COCS and (II) Perspectives for minimizing the risk of VTE.

COCs have been on the market since the 1960s, and the first case of thrombosis occurred in the same decade. Most contraceptives have a combination of estrogen (mestranol or ethinylestradiol) and progesterone, with ethinylestradiol (EE) being considered the component most at risk for venous thrombosis in users (GIALERAKI et al, 2018; KHALANI et al, 2020).

The aforementioned authors also state that COCs cause various alterations in the procoagulant, anticoagulant and fibrinolytic pathways.

As a result, there is a consensus about the greater likelihood of developing venous thromboembolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE) from its use. In addition, in rarer cases, it can cause arterial thrombosis (TRAVEN et al, 2021; EMMERSON et al, 2018; SUGIURA et al, 2018; DRAGOMAN et al, 2018).

In this sense, the duration of contraceptive use as well as the generation of progesterone and the dose of estrogen in the COC have a clear influence on the risk of developing thrombosis. The risk of developing VTE is higher during the first 6 to 12 months after starting treatment, increasing from the fourth month of



administration, but it is worth noting that the use of the third generation of progestins has a greater effect than the first (GIALERAKI et al, 2018; SWANEPOEL et al, 2018).

Similarly, EE in COCs increases the levels of procoagulant factors such as fibrinogen, prothrombin and coagulation factors VII, VIII and X and decreases the level of factor V. This is due to the fact that EE has been shown to closely control certain proteins such as protein S and protein C, unlike most progestogens. In addition, it has been observed that the use of two COCs, both containing drospirenone (DRSP) and EE, cause spontaneous fibrin formation in whole blood and a change in fiber morphology (EMMERSON et al., 2018; GIALERAKI et al., 2018; KHALANI et al., 2020; SWANEPOEL, 2020).

There are alterations and an aggregation of erythrocytes, mainly by the combined DRSP/20EE® and DRSP/30EE®, accompanied by the spontaneous formation of a fibrin network that causes the occurrence of clots, which leads to occlusions in the vascular system. Therefore, the increased risk of VTE associated with these COCs can be explained by these clots rich in erythrocytes and fibrin that occlude the venous vessels (SWANEPOEL et al., 2018; EMMERSON et al., 2018).

In this context, the risk of VTE associated with COC use is two to four times higher than in non-users, with an estimated incidence of 7-10 per 10,000 women per year compared to between 1 and 4 per 10,000 in women of reproductive age who do not use oral contraceptives (SWANEPOEL, 2020). Furthermore, if women are still deficient in natural coagulation inhibitors (antithrombin, protein C and protein S), the incidence is 2 to 9 times higher than in women with these deficiencies who do not use them (GIALERAKI et al., 2018).

Newer types of COCs containing the estrogen component estradiol appear to have a lower risk of VTE than COCs containing EE as well as initial attempts to lower the risk were made by reducing the dose of estrogen in COCs, which in fact led to a reduced risk of VTE (KHALANI et al., 2020).

Likewise, the combination of COCs containing second-generation progestogens (levonorgestrel) and estrogen is the safest choice for preventing venous and arterial events and should be preferred as medication, especially in first-time users (GIALERAKI et al, 2018).

Finally, the unanimous results suggest that there is no statistically significant association between the use of progestogen-only contraceptives and venous thrombosis, except for injectables containing depot medroxyprogesterone acetate (DMPA) (KHALANI et al., 2020).

5 FINAL CONSIDERATIONS

The widespread use and benefits of COCs in women's lives is undeniable, and it is not recommended that they be discontinued in patients at low risk of thromboembolic accidents. However, it is also a fact that the hormones estrogen and progestogen have the ability to amplify blood coagulation, as well as increasing the procoagulant cascade of coagulation, thus intervening in hemostasis.



It is therefore advisable for women who use these drugs to be monitored by a specialized doctor, who will show them their advantages, disadvantages and dosage for rational use, especially for those who have risk factors such as genetic predisposition. Other factors such as age, smoking, extensive surgery, neoplasms, alcoholism, obesity, a sedentary lifestyle and cardiovascular disease should also be taken into account by the professional, as these increase the risk of thrombotic complications.

More scientific evidence is needed to determine more precisely the risk of thromboembolism for combined hormonal formulations, as well as more guidance for the female population in the search for quality and life expectancy. In this way, the use of contraceptives can be made safer, generating great advances and benefits for women, such as autonomy in conception, as well as in the treatment of alterations in menstrual cycles.



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